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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/704,554	11/03/2000	Lawrence Friedhoff	0200-0004	4555

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EXAMINER	
JIANG, SHAOJIA A	
ART UNIT	**PAPER NUMBER**
1617	

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/704,554	FRIEDHOFF ET AL.	
	Examiner	Art Unit	
	Shaojia A. Jiang	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *102-114* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *102-114* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on July 21, 2004 has been entered.

This Office Action is a response to Applicant's request for continued examination (RCE) filed July 21, 2004, and amendment and response to the Final Office Action (mailed August 13, 2003), filed July 21, 2004 wherein claims 84-101 are cancelled, and claims 104-114 are newly submitted.

Currently, claims 102-114 are pending in this application.

Claims 102-114 are examined on the merits herein.

Applicant's amendment filed July 21, 2004 canceling claims 84-93 and amending claim 102 with respect to the objection of claims 84-93, 102 of record in the Office Action dated August 13, 2003 has been fully considered and is found persuasive. Therefore, this objection is withdrawn.

Applicant's amendment filed July 21, 2004 canceling claims 84-101 and amending claims 102-103 with respect to the rejection of claims 84-103 made under 35

U.S.C. 112 second paragraph for the use of the indefinite recitations, of record stated in the Office Action dated August 13, 2003 have been fully considered and found persuasive to remove the rejection. Therefore, the said rejection is withdrawn.

Applicant's amendment filed July 21, 2004 canceling claims 84-90, 92-93 and amending claims 102-103 with respect to the rejection of claims 84-90, 92-93 and 103 made under 35 U.S.C. 102(b) as being anticipated by Scolnick (WO 95/06470) of record in the Office Action dated August 13, 2003 have been considered and found persuasive to remove this particular rejection since claims 84-90, 92-93 are cancelled; claims 102-103 have been amended by adding new limitations into the claims. Therefore, the said rejection is withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 102-103 as amended now new claims 104-114 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's amendment submitted July 21, 2004 with respect to amended claims 102-103 has been fully considered but is deemed to insert new matter into the claims since the specification as originally filed does not provide support for "after oral administration to a human patient releases said at least one HMG-COA reductase inhibitor at a rate to maintain therapeutically effective levels over a 24 hour dosing interval, and continuing treatment with said controlled release formulation to effect a decrease in mean beta amyloid concentration in the blood of said human patient by at least about **18 pg/ml** after 1 month of treatment".

These new recitations read on that each and every patient's beta amyloid concentration after oral administration of the particular HMG-CoA inhibitor composition for 1 month reduces at least about 18/pg/ml. The original specification merely discloses the testing data showing that some particular patients' beta amyloid concentrations decreased at least about 18/pg/ml after 1 month of treatment (see Table 9 at page 41), whereas others' beta amyloid concentrations did not reduce as claimed herein. Nowhere can the recitation be found in the specification.

Consequently, there is nothing within the instant specification which would lead the artisan in the field to believe that Applicant was in possession of the invention as it is now claimed. See *Vas-Cath Inc. v. Mahurkar*, 19 USPQ 2d 1111, CAFC 1991, see also *In re Winkhaus*, 188 USPQ 129, CCPA 1975.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 102-105, 108-110 and 113-114 are rejected under 35 U.S.C. 112, first paragraph, for scope of enablement because the specification, while being enabling for the particular agents such as HMG-COA reductase inhibitor selected from the group consisting of mevastatin, pravastatin, simvastatin, atolwastatin, lovastatin, rivastatin, fluvastatin disclosed in the specification employed in methods for treatments of Alzheimer's disease or Down's syndrome, does not reasonably provide enablement for the employment any HMG-COA reductase inhibitors, to be administered for the claimed methods of the particular treatments herein, i.e., Alzheimer's disease in a patient.

These recitation, "one HMG-COA reductase inhibitor", in these claims, is seen to be merely functional language.

The instant specification fails to provide information that would allow the skilled artisan to fully practice the instant invention without ***undue experimentation***. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims;

(6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

The nature of the invention: The instant invention pertains to in methods for treatments of Alzheimer's disease or Down's syndrome in a patient.

The relative skill of those in the art: The relative skill of those in the art is high.

The breadth of the claims: The instant claims are deemed very broad since these claims reads on any HMG-COA reductase inhibitors employed in the claimed methods of particular treatment herein.

The amount of direction or guidance presented:

Functional language at the point of novelty, as herein employed by Applicants in claims 1-2, is admonished in *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398 (CAFC, 1997). The CAFC clearly states that "[A] written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition, such as by structure, formula, [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials" at 1405(emphasis added), and that "It does not define any structural features commonly possessed by members of the genus that distinguish from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus.." at 1406 (emphases added).

In the instant case, "one HMG-COA reductase inhibitor", recited in the instant claims is purely functional distinction. Hence, the functional recitation reads on any

compounds that might have the recited functions. However, the specification merely provides those particular compounds for the claimed method of treatment herein (see the specification).

Thus, the instant specification fails to meet the requirements set forth under 35 U.S.C. 112, first paragraph, since it fails to provide those elements required to practice the inventions, nor "inform the public during the life of the patent of the limited of monopoly asserted" (*General Electric Company v. Wabash Appliance Corporation et al.* 37 USPQ at 468 (US Supreme Court 1938)).

The predictability or unpredictability: the instant claimed invention is highly *unpredictable* as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art cannot fully described genus, visualize or recognize the identity of the members of the genus, by structure, formula, or chemical name, of the claimed subject matter, except those particular compounds of formula disclosed in the specification, as discussed above in *University of California v. Eli Lilly and Co.* Hence, in the absence of fully recognizing the identity of the members genus herein, one of skill in the art would be unable to fully predict possible physiological activities of any compounds having claimed functional properties in the claimed method of treatment herein.

Moreover, one of skill in the art would recognize that it is highly unpredictable in regard to therapeutic effects for treatments of Alzheimer's disease or Down's syndrome in a patient, side effects, and especially serious toxicity that may be generated by drug-drug interactions when and/or after administering to a host (e.g., a human) any compounds represented by "one HMG-COA reductase inhibitor", and/or while the patient also administering other medicines. See text book "Goodman & Gilman's The Pharmacological Basis of Therapeutics" regarding possible drug-drug interactions (9th ed, 1996) page 51 in particular. This book teaches that "The frequency of significant beneficial or adverse drug interactions is unknown" (see the bottom of the left column of page 51) and that "Recognition of beneficial effects and recognition of and prevention of adverse drug interactions require a thorough knowledge of the intended and possible effects of drugs that are prescribed" and that "The most important adverse drug-drug interactions occur with drugs that have serious toxicity and a low therapeutic index, such that relatively small changes in drug level can have significant adverse consequences" (see the right column of page 51) (emphases added).

In the instant case, in the absence of fully recognizing the identity of the members genus herein except those particular compounds of formula in the specification, one of skill in the art would not be able to fully predict the possible treatments herein and possible adverse effects occurring with many compounds having claimed functional properties and their combinations to be administered to a host in the claimed method herein. Thus, the teachings of the "Goodman & Gilman's" book clearly support that the instant claimed invention is highly unpredictable.

The presence or absence of working examples and the quantity of experimentation necessary:

It is noted that only particular HMG-COA reductase inhibitor, lovastatin, is employed in working examples of the specification. Thus, the specification fails to provide clear and convincing evidence in sufficient support of the broad use of any compounds having those functions recited in the instant claims. As a result, necessitating one of skill to perform an exhaustive search for the embodiments of any compounds having those functions recited in the instant claims suitable to practice the claimed invention.

Genentech, 108 F.3d at 1366, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the *Wands* factors, the case *University of California v. Eli Lilly and Co.* (CAFC, 1997) and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in *undue experimentation* to test all compounds encompassed in the instant claims and their combinations to be administered to a host employed in the claimed methods of the particular treatments herein, with no assurance of success.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation "wherein said HMG-COA reductase inhibitor comprises lovastatin acid" renders the claim indefinite since "HMG-COA reductase inhibitor is lovastatin acid" as recited in claim 107, but not "comprises".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 102-114 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scolnick (WO 95/06470) in view of Chen et al. (5,916,595, of record) and McKhann et al. (of record).

Scolnick discloses methods of treating Alzheimer's disease or the onset of Alzheimer's disease in a human patient comprising administering to the said patient the instant therapeutically effective amount of a composition comprising an HMG-CoA reductase inhibitor (see page 11 line 14-15), in particular, lovastatin (20 mg per day, see Example 1 at page 11), simvastatin, pravastatin, and fluvastatin. Scolnick also discloses

that the HMG-CoA reductase inhibitor is administered orally by a time-controlled release dosage form including osmotic devices, diffusion controlled systems, dissolution controlled matrices and erodible/degradable matrics (see particularly page 11 lines 8-11 and claim 22). Note that the therapeutically effective amount of the HMG-CoA reductase inhibitor to be administered per day in the instant invention has been disclosed in Scolnick (see page 11 line 14-15 and Example at page 11). See also abstract, page 2 lines 16-20, page 10, and claims 1-25. Scolnick further discloses that the treatment therein with the lovastatin composition underwent four consecutive nine-week periods, within the instant claimed period (see Example 1 at page 11).

Note that both Alzheimer's disease and Down's syndrome in a human who exhibits symptoms are known as amyloid precursor protein processing disorders.

Scolnick does not expressly the employment of the controlled release formulation of HMG-CoA reductase inhibitor comprising an osmotic agent and coating agents with a pH sensitive water insoluble polymer. Scolnick does not also expressly the methods therein further comprising a step for determining whether a human exhibits at lease one symptom of Alzheimer's disease.

Chen et al. discloses that the controlled release formulation of HMG-CoA reductase inhibitor, lovastatin in particular, comprising an alkyl ester of a substituted naphthalene, and an osmotic agent and coating agents with a pH sensitive water insoluble polymer (see abstract, Example 1-3 at col.6-8, and claims 1-12) is a better controlled release system and has advantages, e.g., substantially and completely delivering a HMG-CoA reductase inhibitor, lovastatin in particular without the need to

provide a passageway, and additionally providing higher bioavailability (see col.2 lines 5-14).

McKhann et al. teaches that a method for determining whether a human exhibits at lease one symptom of Alzheimer's disease Alzheimer's disease is well known in the art (see the entire article of McKhann et al. and as Applicant admitted at page 11 lines 16-23 of the specification herein).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ the controlled release formulation of HMG-CoA reductase inhibitor, disclosed in Chen at el., comprising an alkyl ester of a substituted naphthalene, and an osmotic agent and coating agents with a pH sensitive water insoluble polymer, and to employ the method for determining whether a human exhibits at lease one symptom of Alzheimer's disease taught in McKhann et al. in the instant claimed methods.

One having ordinary skill in the art at the time the invention was made would have been motivated to employ the controlled release formulation of HMG-CoA reductase inhibitor, disclosed in Chen at el., comprising an alkyl ester of a substituted naphthalene, and an osmotic agent and coating agents with a pH sensitive water insoluble polymer, in the instant claimed methods, because the controlled release formulation of Chen at el. is known to be a better controlled release system and have advantages, e.g., substantially and completely delivering a HMG-CoA reductase inhibitor, lovastatin in particular without the need to provide a passageway, and additionally providing higher bioavailability.

Moreover, one having ordinary skill in the art at the time the invention was made would have been motivated to employ a method step for determining whether a human exhibits at lease one symptom of Alzheimer's disease in the instant claimed methods since a method for determining whether a human exhibits at lease one symptom of Alzheimer's disease is well known in the art, i.e., taught in McKhann et al. Thus, it is well within the skill of artisan to determine whether a human exhibits at lease one symptom of Alzheimer's disease using the known method and then treat the patient.

Thus the claimed invention as a whole is clearly prima facie obvious over the combined teachings of the prior art.

Applicant's remarks filed on June 21, 2004 with respect to the rejection of claims 84-90, 92-93 and 103 made under 35 U.S.C. 103(a) of record in the previous Office Action August 13, 2003 have been fully considered but are moot in view of the new ground(s) of rejection above and also because claims 84-90, 92-93 are cancelled and claim 103 is amended by Applicants.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double

patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 102-114 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8, 10-12, and 41-45 of copending Application No. 10/067,593.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application is drawn to the method of for managing a patient with Alzheimer's disease or at risk of developing Alzheimer's disease comprising administering the same agent as the instant claim and the method steps are substantially similar to the instant claims.

Thus, the claimed method in copending Application No. 10/031149 and the instant claimed method are seen to substantially overlap.

Thus, the instant claims are deemed to be anticipated by the claims 1-8, 10-12, and 41-45 of copending Application No. 10/067,593.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

In view of the rejections to the pending claims set forth above, no claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Jiang, whose telephone number is (571)272-0627. The examiner can normally be reached on Monday-Friday from 9:00 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, Ph.D., can be reached on (571)272-0629. The fax phone number for the organization where this application or proceeding is assigned is 703.872.9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

S. Anna Jiang, Ph.D.
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September 1, 2004